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Nocturia is an independent predictive factor of prevalent hypertension in obstructive sleep apnea patients

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Keywords: Obstructive sleep apnea; hypertension; nocturia; cardiovascular risk.

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HIGHLIGHTS

- Nocturia was associated with prevalent hypertension after adjustment.
- This association exhibited a dose-response relationship for all the strates of age.
- The strength of the association was enhanced for patients over 64 years.
- Nocturia is a strong independent predictor of prevalent hypertension in OSA.

ABSTRACT

Objective: To determine whether nocturia is an independent predictor for prevalent hypertension in obstructive sleep apnea (OSA).

Methods: We analyzed data from a national prospective clinical cohort of OSA patients participating in the French national prospective registry. Anthropometric data, co-morbidities, OSA severity and number of voids/night were included in multivariate analysis to determine the independent variables associated with prevalent hypertension.

Results: 22,674 OSA patients were included, 11,332 were hypertensive. The prevalence of hypertension among OSA patients was about 1.3 times higher in patients suffering from nocturia, with a prevalence of nocturia of 61.45% versus 46.52% in hypertensive and in non-hypertensive OSA patients ($p<0.001$). There was a significant positive relationship between hypertension and the severity of nocturia beyond 2 voids/night: 2 voids/night versus 0: OR=1.270 (CI95%=1.175; 1.372), 3 voids/night versus 0: OR=1.422 (95%CI=1.293; 1.565) and 4 voids/night versus 0: OR=1.575 (95%CI=1.394; 1.781). The strength of the association was enhanced for patients over 64 years.

Conclusions: Nocturia is a strong independent predictor of prevalent hypertension in OSA. This association exhibited a 'dose-response' relationship beyond 2 voids/night. The resolution of nocturia after continuous positive airway pressure (CPAP) treatment might be an important outcome to consider for the response of hypertension to CPAP.

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INTRODUCTION

Nocturia is defined as waking at night one or more times in order to void and returning to sleep [1]. This is a common complaint with a prevalence that increases with age (27% in men younger than 40 years, 41.7% in men older than 60 years) [2] and is the most frequent cause of nocturnal wakening in the general U.S population (75.5%) [3]. Thereby, nocturia is associated with a poorer quality of life mainly explained by sleep loss and daytime sleepiness,[4-6] with an increased prevalence of depressive symptoms [7-9], and a risk of falls and fractures in older patients [9].

In addition, data from the National Health and Nutrition Examination Survey III has shown nocturia to be a major predictor of mortality [10]. This increased mortality rate is certainly due to the association of nocturia and cardio-vascular morbidities, such as diabetes, cardiac disease [11], stroke and hypertension. The prevalence of hypertension in patients with nocturia is 10% higher [12, 13] with a non-dipping pattern during sleep in ambulatory blood pressure (BP) monitoring [13]. Interestingly, nocturia is a common symptom of sleep apnea syndrome (SAS), however the association between nocturia and cardio-vascular disease remained even after adjustment for SAS and other confounding factors [14].

In this context, we sought to determine whether nocturia is one of feature that predicts the occurrence of hypertension in Obstructive Sleep Apnea (OSA). To accomplish this aim

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we performed a cross-sectional analysis of a large national cohort of patients with OSA that contains information on anthropometrics, co-morbidities, OSA and nocturia severity. We hypothesized that nocturia was independently associated with prevalent hypertension in OSA patients with a 'dose-response' type relationship.

METHODS

Study population and data source

We report a cross sectional analysis of data from a prospective national cohort, using the research database of the "Observatoire Sommeil de la Fédération de Pneumologie" (OSFP) (www.osfp.fr; Date of consultation: May 6, 2013). The OSFP is a high quality standardized web-based report, administered by the French Federation of Pneumology. It contains anonymized longitudinal data from patients complaining of sleep disorders, completed and validated by respiratory physicians; recorded by more than 500 respiratory physicians in private practice, general hospitals and university hospitals. Periodic quality control checks are performed to ensure up-to-standard data recording. Ethical committee approval for setting up the database was obtained from "Le Comité consultatif sur le traitement de l'information en matière de recherche en santé" (C.C.T.I.R.S n° 09.521) and authorization from the "Commission Nationale Informatique et Liberté" (C.N.I.L), the French information technology and personal data protection authority. The OSFP Independent Scientific Advisory Committee approved data use for this study. All patients included in the database gave written informed consent.

Data collection and outcome

Patients, over 18 years of age, who had a baseline medical visit reported in the OSFP database were screened for:

-Diagnosis of obstructive sleep apnea syndrome (Apnea/Hypopnea Index (AHI) ≥ 15 events/hour or Oxygen Desaturation Index (ODI) ≥ 10 events/hour)

- Number of voids/night

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-Valid clinical blood pressure measurements

Patients were excluded from the studied population if they had central sleep apnea syndrome or obesity hypoventilation syndrome. Patients' visits and clinical information collected in the OSFP includes diagnoses, symptoms, procedures (i.e., respiratory polygraphy or polysomnography), and the prescriptions issued at the first visit. Anthropometric data, Epworth Sleepiness Scale (ESS) [15], Pichot fatigue scale and the Pichot depression scale [16, 17] scores are also recorded.

Nocturia was defined as waking at night one or more times to void. For each subject, the number of voids/night was specified.

Hypertension was defined as systolic blood pressure/diastolic blood pressure > 140/90 mmHg or as hypertension self-reported by the patient and confirmed by their respiratory physician.

Statistical Analysis

Data were analyzed using Statistical Analysis System (SAS®) software version 9.1.3 (SAS Institute, Cary, NC, USA). Continuous data were expressed as mean (SD) or median (IQR) and categorical data as percentage.

Univariate conditional logistic regression models were used to compare all the variables between hypertensive and non-hypertensive OSA patients. When the log-linearity of a continuous variable was not respected, the variable was converted to categorical data (with quartiles).

Variables which were associated with the risk of being hypertensive in univariate analysis ($p<0.05$) were included in a multivariable conditional logistic regression model (backward selection). In this model testing nocturia and Hypertension, co-variable were age, sex, BMI, alcohol consumption, AHI (total test and 24/h – 34/h vs. < 24/h, 34/h – 50/h vs. < 24/h, ≥ 50/h vs. < 24/h, COPD, myocardial infarction, coronary heart disease, heart failure, arrhythmias, stroke, gastro-oesophageal reflux, diabetes (total and type 1 versus 0, type 2 versus 0), hypercholesterolemia, hypertriglyceridemia and depression. Co-linearity between

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variables was verified by Pearson's coefficient, Spearman's coefficient or Cramer's V2. The variables with >15% of missing data were not included in the logistic regression. The missing values (when < 15%) were replaced by the variable's median for continuous data and for categorical data by the most frequent value.

For all tests, a significance threshold of $p \leq 0.05$ was used.

Since, our population did not express a normal distribution of OSA severity three tertiles of severity were defined (AHI<24/h; 24/h-50/h and AHI ≥ 50/h). As a consequence, the severity limits do not fit with the classical definition of mild, moderate and severe OSA.

RESULTS

Study Flow

Among patients included in the database, 24,627 patients had a diagnosis of OSAS with AHI ≥ 15/h or ODI ≥ 10/h and 22,674 had sufficient data available to study the relationship between the severity of nocturia and OSA-related prevalent hypertension (Figure 1). 11,332 OSA patients exhibited prevalent hypertension.

Patients' characteristics

The baseline characteristics of the studied population are shown in Table 1 for the group as a whole. The patients had a mean age of 57.47 ± 12.86 years, mean BMI of 31.84 ± 6.68 kg/m^2 and a mean AHI of 39.20 ± 19.53 events/hour; 72.66% of them were male.

Hypertension was present in 44.30% and hypercholesterolemia in 27.80% of the included patients. Their mean systolic blood pressure was 134.49 ± 15.65 mmHg and their mean diastolic blood pressure was 79.51 ± 11.04 mmHg.

Nocturia was reported by 53.98% of the patients, with a mean of 1.21 ± 1.40 voids/night, and a minimum of 0 and maximum of 6 voids/night.

Factors associated with hypertension (univariate)

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Among the 22,674 patents with OSA, 11,332 patients had prevalent hypertension. Table 2 compares characteristics of hypertensive and non-hypertensive patients.

Compared to non-hypertensive patients those with hypertension were more likely to be older (60.91 ± 11.60 years versus 54.02 ± 13.14 years, OR=1.039, 95%CI=1.034; 1.044 for one unit increase in age) and more obese (BMI 32.91 ± 6.54 versus 30.76 ± 6.65 kg/m^2, OR=1.069, 95%CI=1.064; 1.073 for one unit increase in BMI).

As expected, prevalent hypertension was significantly associated with cardiovascular co-morbidities: myocardial infarction (OR=1.529; 95%CI= 1.322; 1.769), heart failure (OR=1.552; 95%CI=1.308; 1.842), coronary heart disease (OR=1.599; 95%CI=1.411; 1.813), stroke (OR=1.810; 95%CI=1.532; 2.138), and arrhythmias (OR=1.425; 95%CI=1.287; 1.578) and with metabolic disorders: diabetes (20.60% versus 6.90%) in particular type 2 diabetes type 2 (OR=3.309; 95%CI=2.998; 3.652), and dyslipidemia.

Others co-morbidities/conditions associated with hypertension were alcohol consumption (OR=1.397; 95%CI=1.220; 1.600), COPD (OR=1.166; 95%CI=1.035; 1.314) (but not active smoking), depression and gastro-oesophageal reflux.

The prevalence of hypertension among OSA patients was about 1.3 times higher in individuals suffering from nocturia, since 61.45% of hypertensive patients had nocturia versus 46.52% of non-hypertensives ($p<0.001$). Moreover, there was a significant 'dose response' type relationship between prevalent hypertension and the severity of nocturia: 2 voids/night versus none: OR=1.547 (95%CI=1.438; 1.665), 3 voids/night versus none: OR=1.855 (95%CI=1.696; 2.030) and 4 or more voids/night versus none: OR=2.275 (95% CI=2.027; 2.552).

We also found a significantly higher AHI in hypertensive OSA patients than in non-hypertensives: 40.82 ± 19.80 versus 37.54 ± 19.11 ($p<0.0001$). As demonstrated with nocturia, prevalent hypertension was associated with the severity of sleep apnea syndrome

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(SAS): AHI 34/h-50/h versus AHI < 24/h: OR=1.244 (95%CI=1.146; 1.350) and AHI ≥ 50/h versus AHI < 24/h: OR=1.570 (95%IC=1.445; 1.705).

Factors associated with hypertension (multivariate)

The following factors were included in the multivariate analysis: nocturia (total and 1 versus 0, 2 versus 0, 3 versus 0, ≥ 4 voids/night versus 0), age, sex, BMI, alcohol consumption, AHI (total test and 24/h – 34/h vs. < 24/h, 34/h – 50/h vs. < 24/h, ≥ 50/h vs. < 24/h, COPD, myocardial infarction, coronary heart disease, heart failure, arrhythmias, stroke, gastro-oesophageal reflux, diabetes (total and type 1 versus 0, type 2 versus 0), hypercholesterolemia, hypertriglyceridemia and depression. Prevalent hypertension in OSA patients was associated with being older, a higher BMI, cardio-vascular co-morbidities (coronary heart disease, arrhythmias, stroke, diabetes and dyslipidemia) and also with alcohol consumption and gastro-oesophageal reflux. Figure 2 shows these results.

Nocturia also remained an independent predictor of prevalent hypertension for all the strates of age strata (p<0.001).

In overall analysis, the strength of its association with hypertension, was directly proportional to its severity beyond 2 voids/night: 1 void/night versus 0: OR=1.284 (95%CI=1.184; 1.393), 2 voids/night versus 0: OR=1.270 (CI95%=1.175; 1.372), 3 voids/night versus 0: OR=1.422 (95%CI=1.293; 1.565) and 4 or more voids/night versus 0: OR=1.575 (95%CI=1.394; 1.781) (Figure 3).

The strength of the association was enhanced for OSA patients over the age of 64 years: 1 void/night 1 versus 0: OR=1.418 (95%CI=1.225; 1.642), 4 1 void/night versus 0: OR=1.795 (95%CI=1.472; 2.188).

DISCUSSION

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In a large national cohort of OSA patients, nocturia was associated with prevalent hypertension after adjustment for confounders. This association was found for all age strata and exhibited a dose-response relationship beyond 2 voids/night in overall analysis.

Although nocturnal voiding is frequently attributed to urologic disorders, nocturia is among the main symptoms of sleep-disordered breathing [18]. In our French national registry, the frequency of nocturia was up to 54% among OSA patients with a mean of 1.21 ± 1.40 voids/night. A cross-sectional analysis of the Sleep Heart Health Study in a middle-aged to elderly community-based population has shown that nocturia is independently associated with sleep-disordered breathing and its severity [14]. Intermittent hypoxia, the landmark of OSA, sympathetic hyperactivity and variations in intra thoracic pressure posed against upper airway collapse underlie an increased secretion of natriuretic hormones and thereby favor nocturia [19, 20]. In OSA patients, the bothersome symptoms of nocturia are associated with subjectively disturbed sleep, self-reported excessive daytime sleepiness and has also been also demonstrated to induce adverse objective alterations of sleep patterns as measured by polysomnography [14]. Apart from its impact on quality of life it was important to address whether nocturia has a specific impact on the occurrence of sleep apnea co-morbidities and in particular hypertension.

Several mechanisms have been proposed that could link the recurrent nocturnal cycles of hypoxia/reoxygenation and OSA-related hypertension. Sleep apnea promotes oxidative stress and low grade inflammation [21] which are the initiators of a pathophysiological cascade leading to sympathetic overactivity. The high sympathetic vascular tone exhibited by OSA patient's results in elevated systemic resistance and, hence, elevated blood pressure. Healthy volunteers exposed to 2 weeks of intermittent hypoxia demonstrate an increased sympathetic tone and elevated ambulatory 24 hour blood pressure [22]. On the other hand, increased sympathetic outflow to the kidney stimulates renin release and leads to elevated circulating levels of angiotensin II and aldosterone showing that the renin-angiotensin system is involved in OSA-related hypertension and could be targeted to treat OSA-related hypertension [23]. Our study, clearly demonstrates that after adjustment

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for confounders nocturia also is strongly associated with OSA-related hypertension. Nocturia is a symptom without a cause-effect relationship with hypertension but as consequence it may trigger to new specific mechanistic pathway for the occurrence of hypertension in OSA patients [24]. First, nocturia disturbs sleep and any deterioration in the quality or quantity of sleep is associated with an increase in nocturnal blood pressure which could contribute to the development of daytime hypertension. Shorter sleep duration and/or poor sleep quality are associated with prevalent or incident hypertension but age, gender, environmental exposure and ethnic variations are clear confounders [25]. In our study we have taken into account these confounders. OSA and nocturia, accompanying OSA in more than 50 of the patients, may have synergistic deleterious effects on both sleep duration/quality and blood pressure. In normal individuals, the BP profile is characterized by a 10% fall in mean systolic BP values during sleep compared to when awake, which is termed the normal “dipping pattern” of BP at night. The use of ambulatory BP monitoring (ABPM) has allowed to demonstrate that hypertension in OSA is primarily diastolic and nocturnal with a highly frequent non-dipping pattern [26,27]. Nocturia is associated with non-dipping BP at night and this appears to be mediated by increased nocturnal activity [13].There is growing evidence that the mean nocturnal BP level is a major predictor of cardiovascular morbidity and mortality irrespective of the 24-hour BP levels [28, 29] and this may partly account for the relationship between nocturia and cardiovascular morbidity and mortality.

This study has several strengths, including a prospective design and a large, diverse sample of OSA patients followed by both physicians in private practice or in general and university hospitals in France. Thus we can anticipate widespread generalizability of the study results. However, the findings of this study should be considered in the light of a number of limitations. First, we did not control for the presence of some of the other causes of nocturia such as benign prostatic hypertrophy or excessive evening intake of fluid. However, our data accounted for other classical causes for nocturia such as cardiac failure, ageing, obesity, other sleep problems or excessive alcohol consumption. Second, our cross-sectional study design demonstrating the association between nocturia and OSA-related

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hypertension does not necessarily imply a cause-effect relationship. However the population studied is the largest one in the field and the analysis is strengthened by accounting for the confounding influence of other classical determinants of hypertension.

Conclusion and perspectives

Nocturia is a strong independent predictor of prevalent hypertension in OSA patients. The association between nocturia and cardio-vascular diseases has been demonstrated as persisting even after adjustment for OSA [14]. Thus, the resolution of nocturia after CPAP treatment [30] might be an important outcome to consider for predicting BP response to this therapy and the risk of long term cardiovascular adverse events. In patients with recalcitrant nocturia causes other than OSA should be sought and treated.

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FIGURE LEGENDS

Figure 1. Study Flow chart.

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Body Mass Index (BMI), Apnea-Hypopnea Index (AHI), Oxygen Desaturation Index (ODI), Obstructive Sleep Apnea (OSA).

Figure 2. Multivariate analysis of factors associated with hypertension.

The following factors were included in the multivariate analysis: nocturia (overall test and 1 void/night versus none, 2 voids/night versus none, 3 voids/night versus none, ≥ 4 voids/night versus none), age, sex, BMI, alcohol consumption, AHI (overall test and 24/h – 34/h vs. < 24/h, 34/h – 50/h vs. < 24/h, ≥ 50/h vs. < 24/h, COPD, myocardial infarction, coronary heart disease, heart failure, arrhythmias, stroke, gastro-oesophageal reflux, diabetes (All types and type 1 versus none, type 2 versus none), hypercholesterolemia, hypertriglyceridemia and depression.

Odds ratios for significant variables only are reported.

Coronary Heart Disease (CHD), Body Mass Index (BMI).

Figure 3. Association between nocturia and hypertension, according to severity of nocturia and age.

Data are adjusted for Body Mass Index, alcohol consumption, coronary heart disease, arrhythmia, stroke, gastro-oesophageal reflux, diabetes (Overall test and type 1 versus none, type 2 versus none), hypercholesterolemia and hypertriglyceridemia.

Three age strata were defined as follows:18 to 53 years: n=7477; 54 to 63 years: n=7703; 64 to 100 years: n=7494.

TABLES

Table 1. Main characteristics of the studied population.

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Table 1. Main characteristics of the studied population.

Parameters	Mean ± SD	Median [IQR]	Min	Max
Demographic data				
Age, years	57.47 ± 12.86	57.89 [49.04 ; 66.16]	18.00	100
Gender, % Male	72.66			
BMI, kg/m²	31.84 ± 6.68	30.80 [27.13 ; 35.42]	16.00	77.29
Active smokers, %	15.47			
Alcohol consumption, %	4.21			
AHI, number/h	39.20 ± 19.53	34.00 [24.00 ; 50.00]	15.00	138.00
ODI, number/h	29.40 ± 22.33	23.00 [12.90 ; 40.00]	0	119.84
Nocturia, %	53.98			
Nocturia, number of voids/night	1.21 ± 1.40	1.00 [0.00 ; 2.00]	0	6
Scales				
Pichot depression score	4.10 ± 3.77	3.00 [1.00 ; 7.00]	0	13
Pichot Fatigue score	13.02 ± 8.22	13.00 [6.00 ; 19.00]	0	32
Epworth Sleepiness score	9.92 ± 5.04	10.00 [6.00 ; 13.00]	0	24
Comorbidities, %				
COPD, %	5.52			
Hypertension, %	44.30			
Myocardial infarction, %	3.86			
Coronary heart disease, %	5.45			
Heart failure, %	2.84			
Arrhythmias, %	8.30			
Stroke, %	3.10			
Gastroesophageal reflux, %	15.03			
Diabetes, %	13.74			
Hypercholesterolemia, %	27.80			
Hypertriglyceridemia, %	6.39			
Depression, %	13.51			
Clinical blood pressure				
SBP, mmHg	134.49 ± 15.65	130.00 [122.00 ; 140.00]	80	240
DBP, mmHg	79.51 ± 11.04	80.00 [70.00 ; 85.00]	40	140

Body Mass Index (BMI), Apnea-Hypopnea Index (AHI), Oxygen Desaturation Index (ODI), Chronic Obstructive Pulmonary Disease (COPD), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP).

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Table 2. Comparison between hypertensive and non-hypertensive subjects.

Table 2. Comparison between hypertensive and non-hypertensive patients (Univariate).

Parameters	Non hypertensive patients (n=11 342)	Hypertensive patients (n=11 332)	OR	95% CI	P-Value
Nocturia (Global test)	53.48%	38.55%			<0.0001
1 versus 0	15.62%	16.90%	1.383	1.280 ; 1.495	<0.0001
2 versus 0	17.09%	21.51%	1.547	1.438 ; 1.665	<0.0001
3 versus 0	9.09%	14.16%	1.855	1.696 ; 2.030	<0.0001
≥ 4 versus 0	4.72%	8.88%	2.275	2.027 ; 2.552	<0.0001
Age (increase of 1 unit)	54.02 ± 13.14	60.91 ± 11.60	1.039	1.034 ; 1.044	<0.0001
Women versus Men	26.06%	28.63%	1.102	1.037 ; 1.171	0.0016
BMI	30.76 ± 6.65	32.91 ± 6.54	1.069	1.064 ; 1.073	<0.0001
Active Smokers	17.55%	13.40%	1.008	0.934 ; 1.088	NS
Alcohol	3.50%	4.91%	1.397	1.220 ; 1.600	<0.0001
AHI (Global test)	37.54 ± 19.11	40.82 ± 19.80			<0.0001
24/h – 34/h vs. < 24/h			1.134	1.045 ; 1.230	0.0026
34/h – 50/h *vs*. < 24/h			1.244	1.146 ; 1.350	<0.0001
≥ 50/h *vs.* < 24/h			1.570	1.445 ; 1.705	<0.0001
COPD	4.63%	6.42%	1.166	1.035 ; 1.314	0.0116
Myocardial infarction	2.66%	5.06%	1.529	1.322 ; 1.769	<0.0001
Coronary artery disease	3.54%	7.37%	1.599	1.411 ; 1.813	<0.0001
Heart failure	1.85%	3.83%	1.552	1.308 ; 1.842	<0.0001
Arrhythmias	5.89%	10.71%	1.425	1.287 ; 1.578	<0.0001
Stroke	1.89%	4.32%	1.810	1.532 ; 2.138	<0.0001
Gastroesophageal reflux	13.40%	16.66%	1.269	1.177 ; 1.369	<0.0001
Diabetes (Global test)	6.90%	20.60%			<0.0001
T1 versus 0	1.67%	3.93%	2.393	2.006 ; 2.856	<0.0001
T2 versus 0	5.23%	16.67%	3.309	2.998 ; 3.652	<0.0001
Hypercholesterolemia	17.89%	37.71%	2.472	2.320 ; 2.633	<0.0001
Hypertriglyceridemia	4.03%	8.76%	2.241	1.992 ; 2.522	<0.0001
Depression	12.82%	14.20%	1.148	1.060 ; 1.242	0.0006

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Body Mass Index (BMI), Apnea-Hypopnea Index (AHI, Chronic Obstructive Pulmonary Disease (COPD).

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